ORIGINAL

AF/1655

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants:	Castillo et al.
Serial No.:	09/753,313
Title of Invention:	Catechins and Green Tea Extract for the Treatment of Amyloidosis in Alzheimer's Disease and Other Amyloidoses
Filing Date:	12/29/2000
Group Art Unit:	1655
Examiner:	Tate, C.
Attorney Docket No.:	PROTEO.P16

Kirkland, Washington 98034
September 5, 2006

TO THE COMMISSIONER FOR PATENTS
Mail Stop Appeal Brief-Patents
PO Box 1450
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APPEAL BRIEF OF APPELLANT

This is an appeal from the final rejection of the Examiner dated 1/05/2006 rejecting Claims 4, 5, 10 and 28-32. The Notice of Appeal for this case was filed July 5, 2006. Attached is the requisite Brief filing fee check.

REAL PARTY IN INTEREST(37 CFR 41.37 (c)(1)(I))

The patent application in the case appealed is owned by ProteoTech Inc. who is the real party in interest.

RELATED APPEALS AND INTERFERENCES (37 CFR 41.37 (c)(1)(ii))

There are no other related appeals or interferences known to appellant, appellant's legal representative, or assignee.

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CERTIFICATE OF MAILING (37 CFR 1.8A)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D. C. 20231.

September 5, 2006 Patrick Dwyer

STATUS OF CLAIMS (37 CFR 41.37 (c)(1)(iii))

The status of claims on appeal is as follows:

Canceled claims: 1-3, 6-9, 11-27

Pending claims: 4, 5, 10, 28-32

Claims appealed: 4, 5, 10, 28-32

STATUS OF AMENDMENTS (37 CFR 41.37 (c)(1)(iv))

There have been no amendments filed responsive to the Final Rejection; there have been no interviews with the Examiner since the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER (37 CFR 41.37 (c)(1)(v))

The independent claims on appeal are claims 4, 28 and 31; there are no means-plus-function claims. Each claim is reproduced below with references to the subject matter where it appears in the specification by page and line number.

4. A method for the treatment of amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes in a mammalian subject, the method comprising the step of treating amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes by administering to the subject a therapeutic amount of a substance selected from the group of substances consisting of green tea, green tea leaves and green tea extract, such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils [Reference the Specification, page 2, lines 12-23, 24-26 and 30-32; Specification, page 4, lines 21-24; Specification, page 12, line 35 to page 13, line 3; and Figure 1 as described in the Specification, page 31, lines 3-25. References to a "therapeutic amount" may be found in the Specification, page 12, lines 22-33 and page 9, lines 14-17. A discussion of "amyloids" in Alzheimer's disease and type II diabetes may be found in the Specification, page 20, line 1 to page 22, line 4.].

28. A method for the treatment of existing amyloid fibrils in Alzheimer's disease and type II diabetes in a mammalian subject, the method comprising the step of treating or disrupting existing

amyloid fibrils in Alzheimer's disease and type II diabetes by administering to the subject a therapeutic amount of a substance selected from the group of substances consisting of green tea, green tea leaves and green tea extract, such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils [Reference the Specification, page 2, lines 26-30; Specification, page 6, lines 3-8; and Figure 2 as described in the Specification, page 31, line 30 to page 33, line 14. References to a "therapeutic amount" may be found in the Specification, page 12, lines 22-33 and page 9, lines 14-17. A discussion of "amyloids" in Alzheimer's disease and type II diabetes may be found in the Specification, page 20, line 1 to page 22, line 4.].

31. A method for the treatment of amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes in a mammalian subject, the method comprising the step of treating amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes by administering to the subject a therapeutic amount of a substance produced by process have the steps of

(1) water extraction, using water that is not boiling, of a substance selected from the group of substances consisting of green tea, green tea leaves and green tea extract, and

(2) separation and lyophilization of the supernatant from the extraction;

such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils [Reference the Specification, page 10, line 35 to page 11, line 6; Specification, page 11, line 19 to page 12, line12; Specification, page 7, line 26 to page 8, line 10. References to a "therapeutic amount" may be found in the Specification, page 12, lines 22-33 and page 9, lines 14-17. A discussion of "amyloids" in Alzheimer's disease and type II diabetes may be found in the Specification, page 20, line 1 to page 22, line 4.].

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL
(37 CFR 41.37 (c)(1)(vi))

1. Do Claims 4, 5, 10, 28-32 meet the written description requirement of 35 USC 112?

2. Are Claims 4, 5, 28-31 patentable over Mitsui Norin or Takami under 35 USC 102?

3. Are Claims 4, 5, 10, 28-32 patentable over Mitsui Norin and Takami in view of Chatterjee under 35 USC 103?

ARGUMENT (37 CFR 41.37 (c)(1)(vii))

1. Claims 4, 5, 10, 28-32 Meet the Written Description Requirement of 35 USC 112.

Claims 4-5,10 and 28-32 stand rejected under 35 USC §112 as allegedly failing to comply with the written description requirement. The Examiner asserts that the phrase "water that is not boiling" does not appear literally in the specification; however, what does appear in Example 1 is, "extracted in 1 ml of distilled water". Persons skilled in the art would take this statement in the context of its attendant disclosure to mean that the water is not boiling; for boiling water would have been so specified. Claim language does not require a literal antecedent in the specification; a writing which, when read by a person of skill in the art, together with the context of the rest of the disclosure, is sufficient to impart the claimed expression is sufficient.

The Examiner argues that "the specification does not preclude the use of boiling water"; Applicant respectfully points out that no specification can possible preclude everything, and in fact is not required to preclude anything. Specifications by their nature are open disclosures; claims are for preclusion. Persons skilled in the art may certainly use boiling water, but that is not what the specification teaches, and it is not what is claimed. The specification simply teaches the use of distilled water, in its natural and ordinary meaning, which, as persons skilled in the art know, is at room temperature unless otherwise specified.

The Examiner also asserts that the phrase, "such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils" is also not literally present. In addition to the argument presented above as to what a specification in general contains, and what this case specification contains in particular, it is also the case that inferences that may be fairly made by persons skilled in the art from what is written in the disclosure are also adequate support for claimed expressions. In this case, the entire thrust of the disclosure is directed to amyloid

inhibition by the therapeutic amount of substance administered. The claims do no more than make that thrust explicit as a limitation, and are therefore believed to be in compliance with the stated requirement and are therefore patentable. The Examiner's rejection should be reversed.

2. Claims 4, 5, 28-31 Are Patentable over Mitsui Norin or Takami under 35 USC 102.

Claims 4-5, and 28-31 stand rejected under 35 USC §102 as allegedly anticipated by JP 10245342 (Mitsui Norin) or by JP 10-175858 (Takami). The claims require selection of a therapeutic substance that can only be either green tea, green tea leaves or green tea extract, and none of the claims require the use of epicatechin. Independent claims 4, 28 and 31 all now require either green tea, green tea leaves or green tea extract.

Mitsui Norin makes no mention of fibril formation at all (see argument below). Mitsui Norin only teaches narrowly that a certain kind of nerve cell toxicity that is supposedly caused by beta-amyloid protein, can possibly be reduced with tea polyphenols.

Takami also makes no mention of fibril formation at all (see argument below). Takami only teaches narrowly that a certain kind of active oxygen toxicity can be reduced by disclosed extracts of green tea containing various catechins. Nothing beyond a passing reference is said about Alzheimer's disease, and certainly nothing about treating amyloid fibrils.

Wang (Wang, The Neuroprotective Effects of Phytoestrogens on Amyloid ß Protein-induced Toxicity Are Mediated by Abrogating the Activation of Caspase Cascade in Rat Cortical Neurons, J. Biological Chem., vol 276 no 7, pp 5287-5295, February 16, 2001) (copy was attached to 2003 Snow Declaration in this case) reports that "although Aß mediated neurotoxicity [is a] focus of intense interest, the underlying mechanisms are still controversial" (see p 5294, col 2 below fig. 9). Wang thus reports that no necessary inferences may be drawn from any study of Aß mediated neurotoxicity, and the Examiner has cited no authority to the contrary.

Wang also reports that nerve cell death or neurotoxicity is in fact the result of a cascade involving caspases and reactive oxygen species accumulation (see abstract p 5287 - near end). Also, Zhang (Zhang, Selective Cytotoxicity of Intracellular Amyloid ß Peptide 1-42 Through p53

and Bax in Cultured Primary Human Neurons, J. Cell Bio., vol 156 no 3, pp 519-529, February 3, 2002) (copy was attached to 2003 Snow Declaration) reports that nonfibrilized and fibrilized Aß are equally toxic (see p 519, midway thru abstract), and corroborates Wang in suggesting a caspase cell death route (see p 525, col 1, 1st paragraph). This is further refutation of anything that might be regarded as a "necessary" suggestion that inhibition of Aß neurotoxicity may be useful in treating Aß fibril formation, deposition, accumulation and/or persistence. There is likewise no suggestion in any of the literature that fibrillogenesis plays any part whatever in the reported cell death.

Wang even reports that the high antioxidant activity of flavanoids *per se* was not able to protect neurons against Aß-induced neurotoxicity (see p 5292, col 1, end of penultimate paragraph); thus teaching away from a suggestion that flavanoids might be useful in preventing Aß fibrillogenesis.

There are thus no necessary inferences to be drawn from the cited studies pertaining to neuronal cell death or active oxygen reduction as to Aß fibrillogenesis, because in at least some of the reported studies, the causes of the cell death do not involve any effect on Aß fibrillogenesis. There is thus no implication available to serve as a teaching that inhibition of nerve cell death or nerve cell toxicity by Aß inherently leads to treating Aß fibril formation, deposition, accumulation and/or persistence.

Therefore none of the claims inherently read on any of teaching of the cited references. Applicant respectfully submits that the cited doctrine of inherency therefore does not apply to the rejected method claims.

The Federal Circuit is the authority on the subject of inherency. This reviewing court, which sets the law to which both Applicant and the PTO must adhere, has already determined that some kinds of apparent "inherency" do not justify a rejection of claims. *In re Randall Wright*, 848 F.2d 1216, 6 USPQ2d 1959 (Fed.Cir. 1988). The Court says all cases must be decided on their

own facts, and goes on to say, while reversing a PTO inherency rejection of claims not unlike the one presented in this application,

> Thus the question is whether what the inventor did would have been obvious to one of ordinary skill in the art attempting to solve the problem upon which the inventor was working. *Rinehart*, 531 F.2d at 1054, 189 USPQ at 149; see also *In re Benno*, 768 F.2d 1340, 1346, 226 USPQ 683, 687 (Fed.Cir. 1985) ("appellant's problem" and the prior art "present different problems requiring different solutions").
>
> The problem upon which Wright was working was improving the pitch-measuring capability of the level, not the visibility of the bubble. The PTO, having conceded that Wright's structure was unobvious for his intended purpose, erred in holding that this was not relevant. The problem solved by the invention is always relevant. The entirety of a claimed invention, including the combination viewed as a whole, the elements thereof, and the properties and purpose of the invention, must be considered. [Emphasis added]

Wright, 848 F.2d at 1219. Just as in the *Rinehart* and *Wright* cases above, so also in this case, "[Applicant's] problem and the prior art present different problems requiring different solutions". It has to be relevant that the problem solved by Applicant (treatment of amyloid fibrils) is not the problem addressed by the cited references (nerve cell toxicity and cell death). Under the law of the Federal Circuit, which is the law the binds the PTO, the rejected claims are therefore not "inherently" present in the cited references, and they therefore must be allowed over the cited art.

The specific limitations of the rejected claims must therefore all be read in any attempt to read any of the claims upon any prior art methods, and the claimed methods all differ markedly from the teachings of the cited references. The Examiner asserts that the cited references teach the same method steps that are claimed in this case, but that is not so. Each rejected claim is directed to a precise set of steps that is no where disclosed in any of the cited references. The rejected claims are directed to methods of use of therapeutic quantities of disclosed substances to actually interfere with and prevent or reverse amyloid fibril formations. The Examiner asserts that the cited references teach the same method steps that are claimed in this case, but that is not so, since each of the cited references has as its object the therapeutic treatment of a condition that is not the same condition as any of the targets of any of the rejected claims.

It is also necessarily the case that, in the claimed method steps, the step of administering a therapeutic amount (or a therapeutically effective amount) of a selected substance alone is a step that is different from any implied step in any of the cited references, since whatever amount might be therapeutic in treating cell death or neurotoxicity (as taught by Mitsui Norin), or active oxygen (as taught by Takami), is, for reasons already set forth above, not necessarily therapeutic for any of the amyloid fibrillogenesis involved in the therapeutic targets of the rejected claims.

The Examiner also incorrectly characterizes lines 13-16 on page 5 of the specification as an admission of prior art; Applicant discloses that catechins are present in green tea, as part of Applicant's report of it's own discoveries, and does not therein admit that such knowledge was already prior art at the time of disclosure. It is also submitted that the Examiner is reading into the Mitsui Norin reference something more than it actually contains, when he states that it teaches giving green tea extract "to a subject suffering from Alzheimer's disease so as to inhibit senile plaque formation due to deposition of beta-amyloid protein on brain nerve cells" so that the toxicity of beta-amyloid protein is reduced; in fact, Mitsui Norin makes no reference whatever to any of these processes. It is clear that Applicant is the only one disclosing treatment and reduction of amyloid fibrils through the use of green tea extract.

The Examiner simply offers no objective support for his assertion that "the claimed effect would inherently occur upon oral administration of an effective amount of green tea extract, as taught by the cited references." As discussed above, what might be effective for the uses to which the cited reference put green tea, is not demonstrably related to what is effective for inhibiting fibrillogenesis, as claimed. The Examiner's rejection should be reversed.

3. Claims 4, 5, 10, 28-32 Are Patentable over Mitsui Norin and Takami in View of Chatterjee under 35 USC 103.

Claims 4, 5, 10 and 28-32 are also rejected under 35 USC 103 over Mitsui Norin and Takami in view of Chatterjee, and the recognized state of the art; Applicant respectfully traverses these rejections as well. Primarily for reasons already argued above, none of the cited references,

nor any combination of them, make obvious the combination of steps and substances in dependent claims 10, 30 and 32, as no combination of references teaches or suggests all of the steps and substances of these claims. Claims 10, 30 and 32, as properly read, contain all the limitations of there respective parent claims, and as such, all cited references fail to suggest the combination of steps and substances actually claimed.

The 103 reference to Chatterjee adds nothing to the inapplicability of the other cited references, as it teaches only that Gingko biloba has a "stimulating effect on the cholinergic system of the central nervous system", a system which has no demonstrable connection to amyloid fibrillogenesis. Chatterjee is therefore not properly combinable with the other cited references. Chatterjee is also completely silent about any of the other claimed ingredients.

The Examiner's 103 rejection, like the 102 rejection, utterly depends upon his incorrect application of the doctrine of inherency as to the other cited references. For reason argue above and incorporated here as if fully set forth, the rejected claims are therefore all believed to be non-obvious and allowable over the cited art. The Examiner's supposition that any of the listed ingredients are known in the art to be efficacious in treating amyloid fibrils remains unsupported, even with the introduction of Chatterjee. It is Applicant that has discovered this efficacy for these ingredients, and the Examiner cites no reference or authority to the contrary.

Amended Claim 4 recites two distinct method steps not disclosed in any cited reference:

> "the method comprising the step of treating amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes ... " and
>
> "such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils."

The presence of these distinct method steps alone make the cited doctrine of inherency inapplicable, because even if this doctrine could be applied in this case, it could not be applied to

a claimed method where the method steps themselves are not covered in the references. For these additional reasons, Claim 4 and its dependents are all believed to be allowable.

Claim 28 includes an express recitation that the fibrils to be treated are already existing. Claim 28 and its dependents are therefore also believed to be allowable.

Claim 31 includes the express recitation of several new process steps by which the therapeutic substances are to be derived. It is believed that these explicit process steps among others, which are novel over any process disclosed by the cited art, render the claim allowable. Claim 31 now requires that the substances to be administered be created by (1) a water extraction using water that is not boiling of one the substances selected from green tea, green tea leaves, and green tea extract, and (2) separation and lyophilization of the supernatant from the extract. These processes, which are set forth in Example 1 of the specification, are distinct from the extraction processes taught by the references. For instance, in Mitsui in paragraph 0027, the green tea extraction is only taught to proceed either by boiling water extraction or by boiling alcohol or acetone extraction. These are significantly different extraction steps and likely to produce significantly different extracts. Mitsui then teaches separation of the extract by HPLC or by organic solvent dilution. This is a different step entirely from the claimed simple separation of supernatant and lyophilization. Accordingly, Claim 31 is neither anticipated or rendered obvious by any of the cited references. The Examiner's rejection should be reversed.

Respectfully submitted,

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CLAIMS APPENDIX (37 CFR 41.37 (c)(1)(viii))

1-3. Cancelled.

4. A method for the treatment of amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes in a mammalian subject, the method comprising the step of treating amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes by administering to the subject a therapeutic amount of a substance selected from the group of substances consisting of green tea, green tea leaves and green tea extract, such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils.

5. The method of Claim 4, wherein the substance is green tea extract.

6-9. Cancelled.

10. The method of Claim 4 further comprising, in the step of administering the therapeutic substance, additionally administering a therapeutic quantity of a substance selected from the group of substances consisting of, and commonly known as, ginkgo biloba, rosemary, gotu kola, bacopin, and ginseng.

11-27. Cancelled.

28. A method for the treatment of existing amyloid fibrils in Alzheimer's disease and type II diabetes in a mammalian subject, the method comprising the step of treating or disrupting existing amyloid fibrils in Alzheimer's disease and type II diabetes by administering to the subject a therapeutic amount of a substance selected from the group of substances consisting of green tea, green tea leaves and green tea extract, such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils.

29. The method of Claim 28, wherein the substance is green tea extract.

30. The method of Claim 28 further comprising, in the step of administering the therapeutic substance, additionally administering a therapeutic quantity of a substance selected from the group

of substances consisting of, and commonly known as, ginkgo biloba, rosemary, gotu kola, bacopin, and ginseng.

31. A method for the treatment of amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes in a mammalian subject, the method comprising the step of treating amyloid fibril formation, deposition, accumulation, aggregation and/or persistence in Alzheimer's disease and type II diabetes by administering to the subject a therapeutic amount of a substance produced by process have the steps of

(1) water extraction, using water that is not boiling, of a substance selected from the group of substances consisting of green tea, green tea leaves and green tea extract, and

(2) separation and lyophilization of the supernatant from the extraction;

such that it is the therapeutic amount of the substance administered that treats or disrupts the amyloid fibrils.

32. The method of Claim 31 further comprising, in the step of administering the therapeutic substance, additionally administering a therapeutic quantity of a substance selected from the group of substances consisting of, and commonly known as, ginkgo biloba, rosemary, gotu kola, bacopin, and ginseng.

EVIDENCE APPENDIX (37 CFR 41.37 (c)(1)(ix))

Not applicable.

RELATED PROCEEDINGS APPENDIX (37 CFR 41.37 (c)(1)(x))

Not applicable.